REMARKS

Claims 1-16, 18-25 and 28-37 are pending in the application. Claims 5 and 37 have been cancelled by this amendment. Claims 17, 26, and 27 were cancelled previously. Therefore, claims 1-4, 6-16, 18-25, and 28-36 are at issue.

This amendment is submitted in accordance with 37 C.F.R. §1.116(a) and §1.116(b) in order to present the rejected claims in a better form for allowance or appeal. This amendment was not presented earlier because the rejection under 35 U.S.C. §103 is new grounds of rejection. Applicants also believed, and still believe, that the obviousness-type double patenting rejection was fully addressed in Amendment "A" filed September 27, 2004. This amendment should be entered because it places the application in better form for allowance or appeal, and the amendment does not require further searching or present any new issues.

Claim 1 has been amended to incorporate the features of originally filed, and now-cancelled, claim 5. Claim 35 has been amended to correct the dependency of the claim.

I. Request for Withdrawal of Final Rejection

Applicants respectfully request a withdrawal of the finality of the rejection because the present rejection under 35 U.S.C. §103 is a new grounds of rejection that was *not* necessitated by an amendment. Under M.P.E.P. 706.07(a), a final rejection is not

proper when the examiner introduces a new ground of rejection that is neither necessitated by applicants' amendment of the claims nor based on information submitted in an IDS. In particular, in Amendment "A," claim 1 was amended to insert the features of originally filed claim 17. The issuance of a final rejection, therefore, is premature because the examiner issued a *new* ground of rejection on a claim already before the examiner. Accordingly, it is submitted that the final rejection is not in accordance with the well-established practice under M.P.E.P. and, thus, should be withdrawn.

II. Rejection Under 35 U.S.C. §103

Claims 1-16, 18-25, and 28-37 stand rejected under 35 U.S.C. §103 as being unpatentable over WO 97/03675 (WO '675) in view of WO 96/38131 (WO '131 and U.S. Patent No. 4,721,709 ('709). In view of the amendments to the claims and for the reasons set forth below, it is submitted that this rejection should be withdrawn.

The present invention is directed to a pharmaceutical formulation, which exhibits unexpected and surprising results in therapeutic delivery of Compound (A) through enhanced dosage uniformity, stability, and bioavailability. As a result, the present invention achieves a rapid onset of a therapeutic effect, which has been identified as a problem involving the β-carboline (see specification, page 1, lines 16-19; page 2, line 24 through page 3; page 7, lines 21-28). The unexpected and surprising results of the present formu-

lation are achieved because of (i) the presence of Compound (A) as a free drug comprising a particle size of less than about 40 microns *and* (ii) the presence and amounts of other important formulation ingredients, such as a water-soluble diluent, a lubricant, a hydrophilic binder and a disintegrant. The present application specifically discloses that "the particle size of the active compound also has been found to enhance the bioavailability and handling of the present formulation" (see Specification page 8, lines 14-23). The effects and importance of other formulation ingredients are also disclosed in detail, for example, at page 9, lines 24-33; and page 10, lines 16-23. Furthermore, the present invention provides a formulation having improved stability over prior formulations, in addition to improved dissolution and *in vivo* adsorption (page 12, line 32 through page 12, line 2).

Briefly, WO '675 discloses a method treating male erectile dysfunction using Compound (A) and a tablet containing Compound (A), and in particular tablet formulation B.1. at page 13. However, as stated by the examiner, WO '675 fails to teach or suggest use of a free drug form of Compound (A), the particle size of Compound (A), *or* the specifically claimed formulation, let alone all three features.

As stated above, the presently claimed formulations provide a stable composition that effectively delivers the claimed compound (i.e., Compound (A)) *in vivo*. Because Compound (A) is a highly water-insoluble drug, its formulation into a pharmaceutical composition that effectively delivers the drug is not straightfor-

ward. As a result of applicants' investigation, a pharmaceutical composition that is surprisingly physically stable, and that demonstrates improved dissolution and *in vivo* absorption has been achieved.

The differences between WO '675 and the present claims are substantial. First, the presently claimed formulation contains Compound (A) as a free drug in a claimed particle size, whereas WO '675 fails to teach or suggest either of these features of Compound (A). These features, together with the other claimed formulation ingredients, provide the new and unexpected benefits achieved by the presently claimed invention described above.

In addition, the presently claimed formulations, as a whole, are substantially different from the formulations disclosed in WO '675. The following table compares a composition disclosed in WO '675, and relied upon by the examiner, to the presently claimed composition.

Ingredient	**WO '675**[1)]	**Claim 1**
1. Compound (A)	10% w/w	present
2. polyvinyl pyrrolidone (PVP)	30% w/w	present
3. polyethylene glycol (PEG)	10% w/w	not present
4. polysorbate 80	2% w/w	present (claim 3)
5. magnesium stearate colloidal silicon dioxide	0.5% w/w 0.5% w/w	present
6. croscarmellose sodium	5% w/w	present
7. microcrystalline cellulose	42% w/w	present (claim 2)
8. water-soluble diluent	not present	50-80% w/w

1) Formulation B.1. at page 13 of WO '675.

The compositions of WO '675 and claim 1 (or a claim depending therefrom) both include Compound (A), a

wetting agent (e.g., polysorbate 80), a lubricant (magnesium stearate and colloidal silicon dioxide), croscarmellose sodium, and microcrystalline cellulose.

However, the compositions then greatly differ. For example,

(a) the composition of WO '675 contains PEG. Claims 1 and 6 recite a water-soluble diluent, including a polyol, which by definition does not include PEG. See the diluent examples in the specification, and see the definition of a "polyol" previously provided with Amendment "A."

(b) the composition of WO '675 contains 10% w/w PEG, which even if considered a water-soluble diluent, is far below the 50-85% w/w recited in claim 1 for the water-soluble diluent. Furthermore, the water-soluble diluents of the present invention are solids (see claim 7) to effect tablet manufacture. Also, see the specification at page 9, lines 24-30. PEG would not serve in this capacity.

(c) the composition of WO '675 contains 30% w/w PVP. Claim 10 recites 1-5% w/w of a hydrophilic binder, e.g,. PVP. Furthermore, WO '675 fails to teach or suggest a cellulose derivative as the hydrophilic binder.

In view of the above, WO '675 fails to teach the "same" pharmaceutical compositions containing the same active compound and excipients, as asserted by the examiner, and WO '675 has failed to teach or suggest the present invention as a whole. Accordingly, it is submitted that the present invention as a whole would not have been obvious over WO '675.

Moreover, the nonobviousness of the present invention is further demonstrated by the claimed features that the examiner acknowledges are *not* disclosed or suggested in WO '675, i.e., particle size of Compound (A), percentages of ingredients, and amounts of drug in the tablet or capsule (see Office Action, page 3, lines 11-13). The examiner also made an erroneous assumption in reasoning by concluding that WO '675 teaches a free form of Compound (A) because WO '675 fails to disclose an imbedded form of Compound (A). This basis of rejection and reasoning cannot be maintained since it is not in accordance with well-established standard of obviousness test. WO '675 is silent with respect to the form of Compound (A) in the formulation, and thus simply did not disclose this aspect of the present invention.

The secondary WO '131 and '709 references do not overcome the deficiencies of WO '675 for the reasons stated below.

WO '131 is directed to, *and limited to*, improving the bioavailability of poorly water-soluble drugs, like Compound (A), by forming a coprecipitate dispersion. WO '131 explains the problems associated with poorly water-soluble drugs in the free form, e.g., poor bioavailability, and teaches that solid dispersions of a poorly water-soluble drug may overcome these problems. WO '131 then discloses a coprecipitation technique that overcomes the problems associated with poorly water-soluble drugs in the free form and prior solid dispersions. See WO '131, pages 1-4.

WO '131, therefore, merely teaches forming a coprecipitate, and thereby *avoiding* the free form of a poorly water-soluble drug, like Compound (A), to improve dissolution of the drug. WO '131 provides absolutely no teaching or motivation to utilize a free form of Compound (A) in a pharmaceutical formulation to achieve enhanced bioavailability and stability, but rather teaches away from using the free form of Compound (A) to achieve what has achieved by the presently claimed formulation. In fact, it is the problem encountered using a free form of a poorly water soluble drug that WO '131 addresses and attempts to solve.

Although WO '131 provides various examples of pharmaceutical formulations, these formulations contain Compound (A) as a coprecipitate, which again is substantially different from the presently claimed formulations. Therefore, contrary to the examiner's contention, the specific β-carboline coprecipitate compound taught in WO '131 is *different from* the presently claimed free form of Compound (A) in the claimed particle size. In addition, the examiner acknowledges at page 4 of the Office Action that WO '131 "fails to teach the claimed particle sizes," and further, WO '131 fails to suggest using the claimed particle size. Finally, the formulations disclosed in WO '131 at pages 16-19 are substantially different from the presently claimed compositions as a whole.

In view of the above, the cited references, alone or in combination, fail to provide a person skilled in the art a motivation or incentive (a) to incorporate a free form of Compound (A) into a pharma-

ceutical formulation or (b) to provide a free drug of the claimed particle size, let alone utilize *both* of these features, with any reasonable expectation of improving dissolutions and *in vivo* absorption of Compound (A).

Seth et al. '709 also fails to cure the deficiencies of the combined teachings of WO '675 and WO '131. The '709 patent merely teaches fine particle size benzodiazepine drugs *adsorbed* onto a carrier. According to '709 patent, the critical feature of the Seth invention is directed to "the fine particle size of the absorbed hydrophobic drug" (see column 6, lines 13-14). In addition, as stated by the examiner, the "method of Seth comprises the steps of providing dry powder of the insoluble drug that is adsorbed onto a carrier" and "Seth teaches that the drug particles are closely associated with the carrier" (Office Action, page 4). This is in direct contrast to the presently claimed feature of a *free* particle form of Compound (A). The '709 patent simply fails to teach or suggest a free form of the drug, but rather teaches the *necessity and criticality* of adsorbing the drug onto a carrier (see '709 patent, column 4, lines 44-52, for example).

In addition to failing to teach or suggest using a free form of a drug in a formulation, the formulations provided in the '709 patent at columns 9 and 10 are substantially different from the claimed formulations as a whole, and provide no suggestions with respect to modifying formulation ingredients to arrive at the presently claimed formulation. The '709 patent,

therefore, not only fails to teach or suggest a free form of a drug, but also fails to teach or suggest any formulations or formulation modifications that would help overcome the deficiencies of WO '675 and WO '131, taken alone or in combination, to render the present claims obvious. Furthermore, the examiner misapplies applicants' incorporation of U.S. Patent No. 4,605,517 in the present specification ('517) by reference. As specifically stated in the present specification at page 8, lines 28-32, the '517 patent is incorporated by reference *merely* for the purpose of instructing persons reading the present specification how to measure particle size, and, thus, the '517 patent is not referenced for a method of preparing the present formulations. Preparation of the present formulations is illustrated in the examples of the present application, and, thus, do not rely upon the method of U.S. Patent No. 4,605,517.

In summary, for the reasons stated above, the present invention, as a whole, is neither taught nor suggested by any of the cited references, alone or in combination. Accordingly, it is respectfully submitted that the rejection under 35 U.S.C. §103 should be withdrawn.

III. Rejection Under Obviousness-Type Double Patenting

Claims 1-16, 18-25, and 28-37 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Nos. 10/031,531 and 10/031,463. Appli-

cants traverse this rejection and submit that the rejection should be withdrawn.

In issuing an obviousness-type double patenting rejection, it is the *claims* of the present application that must be compared to the *claims* of U.S. Application Nos. 10/031,531 and 10/031,463. Applicants submit that in determining obviousness-type double patenting, the question to be considered is stated in *In re Vogel*, 164 U.S.P.Q. 619, 622 (CCPA 1970), i.e., "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" The CCPA goes on to indicate that, "In considering the question, the patent disclosure may not be used as prior art." For the reasons set forth below, the present obviousness-type double patenting rejection cannot be maintained.

As stated above, the present claims are directed to a pharmaceutical formulation that demonstrates improved dissolution, stability, and *in vivo* absorption of Compound (A). The invention resides in the claimed formulation comprising an active compound provided as a free drug having a certain particle size in combination with additional claimed ingredients, and claimed amounts of ingredients, which achieve this result (see amended claim 1). Among the presently claimed features of the invention are a pharmaceutical formulation containing Compound (A) as a free drug, a small particle size of Compound (A), a solid formulation, a solid tablet, and a capsule containing dry, free-flowing particles of the formulation.

Application No. 10/031,531 is directed to capsules containing a solution or a dispersion of Compound (A). Application No. 10/031,531 has been allowed, and has issued as U.S. patent No. 6,841,167 ('167). All claims in the '167 patent recite a suspension formulation of Compound (A) in specifically claimed solvents and a specifically claimed suspending agent, and are limited to capsules. The subject matter of the allowed '167 claims is completely different from the present claims and patentably distinct, which are directed to *particulate* formulation, tablets containing the formulation and capsules containing dry, free flowing particles of the formulation (see original claim 25). The problem solved in the '167 patent was to solubilize Compound (A) in a solution, or to provide a stable dispersion of Compound (A) in a liquid. Neither of these problems is even addressed or considered in the present application, which is directed to *solid* (particulate) formulations containing Compound (A).

A person skilled in the art could not possibly arrive at a presently claimed composition based on the claims of the '167 patent because a comparison of the '167 patent claims to the presently claimed formulations shows no relation between the compositions. The compositions of the '167 patent claims are totally different from the presently claimed formulations, and the '167 patent claims contain no teachings or suggestions that would lead a person skilled in the art to modify the compositions claimed in '167 patent in a manner that would provide a presently claimed particulate formulation regardless of whether the formu-

lation is a capsule or a tablet. Moreover, the formulations are as fundamentally different as a solid formulation versus a dispersion formulation, before even considering the substantial differences between formulation ingredients as a whole. In addition, the amendment to claim 1 reciting a particulate formulation overcomes the examiner's reasoning at page 8 of the Office Action for maintaining the obviousness-type double patent rejection over the '167 patent.

The claims of application No. 10/031,463, now U.S. Patent No. 6,821,975 ('975), are directed to Compound (A) in a reduced particle size. The present claims are directed to *formulations* containing free Compound (A) having a claimed particle size, *as well as* the ingredients recited in claim 1. The claims of the '975 patent only recite the composition containing the small particle size of Compound (A) and one or more pharmaceutically acceptable carrier, diluent, or excipient. However, these claims fail to recite any *specific* carriers, diluents, or excipients, or the form of formulation (tablet or capsule) as presently claimed. Thus, the '975 patent claims provide no teachings or suggestions that would lead a person skilled in the art to the presently claimed formulations *as a whole*.

Additionally, in applying the test set out in *In re Vogel*, it is submitted that the present claims are patentably distinct and not obvious over the claims of U.S. Patent Nos. 6,841,167 and 6,821,975, which contain claims directed to inventions entirely different from the presently claimed invention. Therefore, it is

submitted that the obviousness-type double patenting rejection of the present claims over the claims of U.S. Patent Nos. 6,841,167 and 6,821,975 is in error and should be withdrawn.

Furthermore, applicants clearly are not attempting to claim related subject matter in order to extend the patent terms of the '167 patent or the '975 patent, which the doctrine of obviousness-type double patenting is intended to present. See, e.g., *In re Kaplan*, 229 U.S.P.Q. 278 (Fed. Cir. 1986). In this case, claims issuing from the present application presumptively will terminate on April 26, 2020 (i.e., twenty years from the filing date of the PCT application upon which the present application is based). The '167 patent claims likewise will terminate on April 26, 2020 because it also is based on a PCT application filed on April 26, 2000 and received no patent term extension. The '975 patent will expire on November 18, 2020, (twenty years after the filing date of the PCT application upon which the patent is based (August 1, 2000) plus a 110-day patent term extension), which is *after* the termination date of any patent issuing from the present application. Accordingly, it cannot be argued that applicants are attempting to extend the patent term of an invention claimed in the '167 and '975 patents, and thus the very reason formed the basis for obviousness-type rejection is vitiated by the above fact.

In summary, it is submitted that the present claims are in a form and scope for allowance. An early

and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP

By 

James J. Napoli
(Registration No. 32,361)
Attorneys for Applicants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606
(312) 474-6300

Chicago, Illinois
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